REMARKS

I. Status of the Claims

Claims 1, 2, 4-14 and 16-23 are pending in the present application. Claims 1, 2, 14, and 17 have been amended. Claim amendments are for the purposes of improved clarity or consistency of claim language unless otherwise noted. No claim amendment should be construed as an acquiescence in any ground of rejection. Claims have been amended without prejudice to pursuing the cancelled subject matter in a continuing application. Support for amended claims 1, 2, 14 and 17 can be found in the specification and claims as originally filed, and for example, on page 14, line 2-3. No new matter has been added by this amendment.

II. The Claims are Patentable under 35 U.S.C. § 112, First Paragraph

Claims 1, 4-14, 16, and 18-23 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for the method, wherein Bst DNA polymerase is involved in a reaction temperature of 80°C.

Claims 1, 2, 14 and 17 have been amended without prejudice to pursuing the cancelled subject matter in a continuing application. Support for claims 1, 2, 14 and 17 as amended can be found in the specification and claims as filed, and for example, on page 14, lines 2-3. Applicants respectfully request that the rejection of claims 1, 4-14, 16, and 18-23 under 35 U.S.C. § 112, first paragraph, be withdrawn.

III. The Claims are Patentable under 35 U.S.C. § 103(a)

Claims 1, 2, 4-14, and 16-23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mack et al., U.S. Patent No. 6,566,502 Bl, in view of Bacallao et al., U.S. Patent No. 7,186,507 B2. The examiner argued that the Mack et al. reference discloses a method of producing cRNA from samples. The examiner further cited the Bacallao et al. reference to disclose a method of generating a plurality of cRNAs, by reverse transcription of a first strand cDNA and use of Bst DNA Polymerase large fragment to produce the second strand of the double stranded cDNA moiety. Applicants traverse the rejection.

Prior art references that serve as the basis of an obviousness rejection must be considered by the examiner in their entirety, *i.e.*, the references must be considered as a whole, including portions that would lead away from the claimed invention. M.P.E.P. 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)). To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify the reference or to combine the reference teachings so as to arrive at the claimed invention and there must be a reasonable expectation of success for achieving the claimed invention as a whole. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

Therefore, to establish a proper *prima facie* rejection, the following elements must be shown:

(1) the references are available as prior art against the claimed invention;

(2) the motivation (explicit or implicit) provided by the references that would have rendered the claimed invention obvious to one of ordinary skill in the art at the time of the invention;

(3) a reasonable expectation of success;

(4) the references teach the claimed invention as a whole.

Takeda Chemical v. Alphapharm Pty., Ltd. 492 F.3d 1350 (Fed Cir. 2007); *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007); *In re Grabiak,* 769 F.2d 729, 733, 226 U.S.P.Q. 870, 873 (Fed. Cir. 1983).

Applicants submit that elements 2 and 4 have not been established. Hence, a *prima facie* obviousness rejection is improper. The examiner has not established a proper *prima facie* case since the combination of references do not teach or suggest the claimed invention as a whole nor is there a motivation to combine the references. The Mack reference in view of the Bacallao reference does not teach or suggest the claimed invention as a whole. The method of producing cRNA of the Mack reference differs from the claimed method for amplifying at least one mRNA in a sample which utilizes Bst DNA polymerase large fragment in combination with a thermostable RNase H for second strand DNA synthesis. By contrast, the Mack reference utilizes a second strand synthesis method known in the art. As applicants point out on page 13, lines 12-22 of the specification, "the Gubler-Hoffman method" utilizes *E. coli* DNA polymerase I, RNase H and *E. coli* DNA ligase I for second strand synthesis, which is the method of the Mack reference. Furthermore the claimed

method for amplifying at least one mRNA in a sample containing a plurality of different mRNAs provides an advantageous result which is not taught or suggested by the Mack reference alone or in combination with the Bacallao reference. In the present claimed methods, a substantial improvement has been made to the second strand cDNA synthesis step by use of thermostable enzymes, *e.g.*, thermostable DNA polymerase and thermostable RNase H. As shown in Table 2 on page 32 of the specification, the claimed second strand synthesis method utilizing Bst DNA polymerase and thermostable RNase H was compared to a second strand synthesis method utilizing *E. coli* DNA polymerase, DNA ligase, and RNase H. The claimed method provided superior yields of cRNA compared to cRNA synthesized by a method utilizing second strand synthesis with *E. coli* DNA polymerase, DNA ligase, and RNase H as taught by the Mack reference, which result is unexpected in view of the prior art as a whole.

The Bacallao reference does not cure the deficiencies of the Mack reference since the Bacallao reference does not teach or suggest a method for amplifying at least one mRNA in a sample containing a plurality of different RNAs comprising in part, utilizing Bst DNA polymerase and thermostable RNase H for second strand synthesis. The examiner incorrectly cited the Baccalao reference in the context of using Bst DNA Polymerase large fragment for second strand DNA synthesis in a method of generating cRNAs. The Bacallao reference provides a method of *in situ* reverse transcriptase polymerase chain reaction (RT-PCR) to amplify mRNA from *in situ* samples. The Bacallao reference provides a second strand synthesis method and exemplifies using Bst DNA polymerase large fragment as a DNA polymerase, in combination with a forward or reverse primer for amplifying cDNA using a PCR reaction. See the Bacallao reference, for example, Col. 2, lines 52-56, and Col. 25, lines 1-4. In particular, the method of the Bacallao reference requires the addition of an exogenous primer, and does not require a thermostable RNase H for second strand DNA synthesis. The Mack reference, in combination with the Bacallao reference, does not teach or suggest a method of generating cRNAs comprising in part, utilizing Bst DNA polymerase and thermostable RNase H for second strand synthesis.

The examiner has not established a proper *prima facie* case since the references do not provide a motivation for one skilled in the art to combine the Mack reference with the Baccalao reference to obtain applicants' claimed invention, a method for amplifying at least

one mRNA in a sample containing a plurality of different RNAs, or a method for comparing the presence or amount of at least one mRNA of interest in a first sample and in a second sample, comprising in part, utilizing Bst DNA polymerase and thermostable RNase H for second strand synthesis. Furthermore, a substantial and unexpected improvement has been made in the yield of cRNA by the use of thermostable enzymes, *e.g.*, thermostable Bst DNA polymerase large fragment and thermostable RNase H in the second strand cDNA synthesis step of the method for amplifying at least one mRNA in a sample. The combination of cited references does not teach or suggest applicants' claimed invention as a whole. Since the claims patentably define over the prior art, Applicants respectfully request that the rejection of claims 1, 2, 4-14, and 16-23 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claims 2 and 17, the combination of the Mack reference with the Bacallao reference does not teach or suggest a method for amplifying at least one mRNA in a sample containing a plurality of different RNAs or a method for comparing the presence or amount of at least one mRNA of interest in a first sample and in a second sample, the first sample and the second sample each containing a plurality of different mRNAs from one or more cells, in part, by synthesizing a second strand of cDNA utilizing a Bst DNA polymerase large fragment and thermostable RNase H at an incubation temperature from 55°C to 70°C. One skilled in the art would not have been motivated to combine the cited references to utilize Bst DNA polymerase large fragment and thermostable RNase H at the indicated incubation temperature for second strand cDNA synthesis, as in the presently claimed method to produce cRNA. Applicants respectfully request that the rejection of claims 2 and 17 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claims 4, 6, and 12, the combination of the Mack reference with the Bacallao reference does not teach or suggest a method for amplifying at least one mRNA in a sample containing a plurality of different RNAs, in part, by synthesizing a second strand of cDNA utilizing a Bst DNA polymerase large fragment and thermostable RNase H at an incubation period of from one to sixty minutes or at an enzyme concentration as claimed. One skilled in the art would not have been motivated to combine the cited references to utilize a concentration of Bst DNA polymerase large fragment and thermostable RNase H for an incubation period as in the claimed method to produce cRNA. Applicants respectfully request that the rejection of claims 4, 6, and 12 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claim 5, the combination of the Mack reference with the Bacallao reference does not teach or suggest a method for amplifying at least one mRNA in a sample containing a plurality of different RNAs, in part, by synthesizing a second strand of cDNA utilizing a Bst DNA polymerase large fragment and thermostable RNase H, and synthesizing RNA utilizing biotin as a label. One skilled in the art would not have been motivated to combine the cited references to obtain the claimed method for amplifying at least one mRNA in a sample containing a plurality of different mRNAs to synthesize cRNA wherein the transcribed RNA is labeled with biotin. Applicants respectfully request that the rejection of claim 5 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claims 7, 8, 9, 10, and 18, the combination of the Mack reference with the Bacallao reference does not teach or suggest a method for amplifying at least one mRNA in a sample containing a plurality of different RNAs, or a method for comparing the presence or amount of at least one mRNA of interest in a first sample and in a second sample, the first sample and the second sample each containing a plurality of different mRNAs from one or more cells, in part, wherein the transcribed RNA is fluorescently labeled, for example with Cy3 or Cy5. As discussed above, one skilled in the art would not have been motivated to combine the cited references to obtain the claimed method for amplifying at least one mRNA in a sample containing a plurality of different mRNAs, in part, utilizing the second strand synthesis method and wherein the transcribed RNA is fluorescently labeled. Applicants respectfully request that the rejection of claims 7, 8, 9, 10, and 18 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claims 11, 22, and 23, one skilled in the art would not have been motivated to combine the cited references to obtain the claimed method for amplifying at least one mRNA in a sample containing a plurality of different RNAs, or the claimed method for comparing the presence or amount of at least one mRNA of interest in a first sample and in a second sample, the first sample and the second sample each containing a plurality of different mRNAs from one or more cells, in part, by synthesizing a second strand of cDNA utilizing a Bst DNA polymerase large fragment and thermostable RNase H, transcribing RNA and determining the presence or absence of a pre-selected target mRNA in the sample; or the claimed method wherein the contacting steps are carried out concurrently; or wherein the first sample contains mRNAs from cells that are pathologically aberrant and wherein said

second sample contains mRNAs from cells that are not pathologically aberrant. Applicants respectfully request that the rejection of claims 11, 22, and 23 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claims 13 and 19-21, one skilled in the art would not have been motivated to combine the cited references to obtain the claimed method for amplifying at least one mRNA in a sample containing a plurality of different RNAs or the claimed method for comparing the presence or amount of at least one mRNA of interest in a first sample and in a second sample, the first sample and the second sample each containing a plurality of different mRNAs from one or more cells, in part, contacting the cRNA produced in the transcribing step (c) with an array containing one or more species of polynucleotide positioned at pre-selected sites on the array, under conditions conducive to hybridization; and detecting any hybridization that occurs between said one or more species of polynucleotide and said cRNA, wherein the array has at least 1,000 polynucleotide probes per square centimeter. Applicants respectfully request that the rejection of claims 13 and 19-21 under 35 U.S.C. § 103(a) be withdrawn.

With regard to claim 16, one skilled in the art would not have been motivated to combine the cited references to obtain the claimed method for amplifying at least one mRNA in a sample containing a plurality of different RNAs, in part, utilizing the second strand synthesis method and wherein the samples employed are from mammalian cells. Applicants respectfully request that the rejection of claims 16 under 35 U.S.C. § 103(a) be withdrawn.

Since the claims patentably define over the prior art, Applicants respectfully request that the rejection of claims 1, 2, 4-14, and 16-23 under 35 U.S.C. § 103(a) be withdrawn.

IV. Conclusion

In view of the foregoing, applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the examiner believes a telephone conference would expedite allowance of this application, please telephone the undersigned at 206-332-1380.

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